A feasibility trial of Cogmed working memory training in fragile X syndrome

Jacky Au*, Laura Berkowitz-Sutherland, Andrea Schneider, Julie B. Schweitzer, David Hessl
and Randi Hagerman
*Department of Pediatrics, Medical Investigation of Neurodevelopmental Disorders (MIND) Institute,
University of California, Davis Medical Center, Sacramento, CA, USA*

Abstract. Individuals with fragile X syndrome (FXS) often present with an array of neurocognitive deficits, particularly in working memory (WM) and other executive functions. Evidence is accumulating that WM training can be effective in certain clinical populations in improving WM abilities and decreasing attention deficit hyperactivity disorder symptoms. We report preliminary findings evaluating the feasibility of Cogmed JM program, a computer-based WM intervention, within the FXS population. Twenty-five participants were evaluated for training. Seventeen were deemed eligible, of whom eight enrolled in the 5-wk training. Baseline characteristics were analyzed, as well as training progress and parental impressions. We conclude that Cogmed JM is a feasible intervention in FXS, though a certain baseline level of ability is required, and urge future controlled trials to determine efficacy.

Keywords: Fragile X syndrome, working memory training, targeted treatments, Cogmed

1. Introduction

Fragile X syndrome (FXS) is a single gene disorder caused by mutation in the fragile X mental retardation 1 (*FMR1*) gene located at Xq27.3, and is the most common cause of inherited intellectual disability (ID). It is caused by a trinucleotide (CGG) repeat expansion at the 5' untranslated region of the *FMR1* gene, which leads to transcriptional silencing and a lack of the fragile X mental retardation protein (FMRP). FMRP, an RNA binding protein, regulates the translation of many other proteins and is vital to proper synaptic function and plasticity [1, 2]. It is also highly expressed in neurons [3]. The lack of FMRP leads to a broad dysregulation of the neurobiological founda-tion of cognition, manifesting in the hallmark cognitive and behavioral deficits of FXS including impairments in working memory, attention, and impulse control [4].

Working memory (WM) is conventionally defined as the ability to store and manipulate cognitive informa-tion for short periods of time [5]. It has both temporal as well as capacity constraints, and plays a vital role in learning and attentional control. Deficits in WM capacity are associated with attention deficit hyperac-tivity disorder (ADHD) [6, 7], and are also common among many neurodevelopmental disorders, including FXS. Contrary to traditional views, recent evidence has accumulated suggesting plasticity of WM. Sev-eral studies have shown that prolonged training with WM-demanding tasks can lead to sustained improve-ments in performance on non-trained WM tasks [8–10]. Correlates of WM plasticity can be seen on a neurochemical level through activation changes with functional magnetic resonance imaging, and dopamine

*Corresponding author: Jacky Au, Department of Education, University of California, Irvine, 3200 Education Building, Irvine, CA 92617, USA. Tel.: +1 916 703 0301; Fax: +1 916 703 0240; E-mail: jwau@uci.edu.

receptor density changes, as well as on a behavioral level through improvements in on-task behavior during a simulated academic task in children with ADHD, and increased attention and focus based on parent reports [11–17]. However, not all researchers are in agreement concerning the success and efficacy of WM training and the extent to which it may generalize to practical skills outside the laboratory is still controversial [18, 19]. Nevertheless, accumulating evidence suggests the possibility of transfer into such practical areas of daily living as academic success, and fluid intelligence [20, 21].

Here we report our preliminary experience in the FXS population using Cogmed JM, a computer-based cognitive intervention designed to improve WM and reduce symptoms of ADHD, which are pervasive in FXS [22, 23]. Though some researchers have already demonstrated improvements in ADHD cohorts after WM training [14, 15, 17, 24], results are mixed [18, 25, 26]. In light of these conflicting reports, some researchers are beginning to elucidate the inter-individual differences that subserve receptivity to cognitive training [27, 28]. This is particularly germane to FXS since there is such a wide spectrum of involvement and varying ability levels. For example, females, who typically have a fully functional *FMR1* gene on their unaffected X chromosome, tend to be higher functioning than their male counterparts [29]. Additionally, FXS tends to be comorbid with other developmental disorders, such as autism spectrum disorders (ASD), and ADHD, which have additive effects on the phenotype [30, 31]. Therefore, the purpose of this preliminary report is to explore the feasibility of cognitive training in FXS, and the factors that may be associated with success, in order to scaffold future studies in this population.

This work is pertinent to other populations with ID as well since most individuals with FXS have ID and face unique challenges. Several cognitive training studies have already been done in cohorts with ID. For example, Van der Molen et al. [32] trained a group of adolescents with mild to borderline ID and found improvements in both verbal and visual short-term memory, as well as transfer into academic achievement such as arithmetic. Söderqvist et al. [28] conducted a similar study with a younger group of children with ID (6–12 yr of age) and found similar results. It should be noted that both these studies used visual WM training tasks (Odd-One-Out and Cogmed JM, respectively), but still found improvements in both visual as well

as verbal non-trained memory tasks, suggesting the possibility of a domain-general transfer. Furthermore, Bennet et al. [33] evaluated Cogmed JM in children with Down syndrome and reported improvements in visual-spatial short-term memory. Given the unique cognitive and behavioral challenges of individuals with FXS, we sought to answer several questions: (1) Can participants understand and comply with the demands of Cogmed working memory training? (2) Are some individuals with FXS more receptive to training than others and can we differentiate the two sub-groups? (3) What are the constraints and parameters of implementing a home-based computer training program with the FXS population? (4) What are parents' perceptions regarding the value of Cogmed training?

2. Materials and methods

2.1. Participant selection

Study participants were recruited from the database of patients and research subjects followed at the University of California Davis MIND Institute Fragile X Research and Treatment Center. Of the individuals we approached, 25 (mean age $\pm$ SD = 11.7 $\pm$ 3.65; 24% female; Table 2) expressed interest and attempted the demonstration program of Cogmed JM. Success with the demonstration program, which was defined as the ability to reliably complete 2-item spans (i.e., reaching threshold for 3-item spans), determined eligibility for further enrollment into the 5-wk training. Regardless of further enrollment into the training, data from these 25 individuals were analyzed to determine group differences between successful and unsuccessful participants.

Of these 25, 17 were eligible for further Cogmed training, but only eight (one female, seven males) were willing to commit to the time and logistical demands of the 5 wk intervention. One participant withdrew early due to oversensitivity to the sound effects, but one participant who was previously unsuccessful with the demonstration program ended up enrolling in the 5-wk training after practicing on the program for 2-wk and demonstrating task competency. We had a net total of eight participants who completed approximately 5-wk of training.

All participants in this study received confirmatory *FMR1* DNA testing at our facility. Study procedures were explained to parents of all participants and they all signed informed consent.

Table 1
Participant demographics*

	Age (yr)	Percent female	Percent ASD	Percent on ADHD medication	FSIQ	WM	VABS-II
Successful ($n = 17$)	12.49 ± 3.05	35%	35%	41%	48.78 ± 6.96	54.22 ± 12.08	68.89 ± 9.21
Unsuccessful ($n = 8$)	10.02 ± 4.15	0%	75%	38%	41.83 ± 4.49	48 ± 0	57.50 ± 13.22
Overall ($n = 25$)	11.70 ± 3.65	24%	48%	40%	46.00 ± 6.88	51.73 ± 9.66	64.33 ± 12.01
P-value	0.16	0.01	0.12	0.89	0.04	0.04	0.04

*Demographic variables of all participants who attempted the Cogmed demonstration program, broken up by participants who were successful and unsuccessful with the demonstration program. Race/Ethnicity breakdown among our total sample of 25 participants are as follows: 76% Caucasian, 2% African-American, 2% Asian, 4% native American, and 12% other. Of those, 32% identified as Hispanic or Latino. The second operand in all fields represents standard deviation. ASD = Autism spectrum disorder; ADHD = Attention deficit hyperactivity disorder; FSIQ = Full scale intelligence quotient; WM = Working memory; VABS-II = Vineland Adaptive Behavior scales – 2nd ed.

Table 2
Spearman correlations of rating scale change scores and Cogmed indices of improvement

Rating scale	Domain	r^*	P^{**}
SNAP-IV	Inattention	0.20	0.64
	Hyperactivity	−0.19	0.65
VAS	Attention	−0.14	0.74
	Hyperactivity	0.17	0.69
	Impulsivity	0.19	0.65
	Forgetfulness	−0.24	0.57
	Organizing thoughts	−0.14	0.74
	Following directions	0.17	0.69
ABC	Irritability	0.39	0.35
	Hyperactivity	−0.04	0.93
	Socially unresponsive/lethargic	−0.07	0.87
	Social avoidance	0.53	0.17
	Stereotypy	0.70	0.05
	Inappropriate speech	0.34	0.42

*All correlation values were re-coded such that positive values denote improvements in behavior corresponding with higher index of improvement scores. However, no values were statistically significant. **The *P*-value of stereotypy is not significant after Boneferroni correction, which would require a significance threshold of $P < 0.01$. SNAP-IV = Swanson, Nolan, and Pelham, Version IV; VAS = Visual Analogue scale; ABC = Aberrant behavior checklist.

2.2. Training program

Cogmed JM rotates through seven games, each requiring serial recall of visuo-spatial information amidst several different WM-challenging contexts. One game also incorporates auditory information. Participants are presented with sequences of varying lengths and asked to recall the sequence by clicking on the appropriate items using a computer mouse. A training meter is presented on screen with a mark that increases or decreases with correct or incorrect responses, respectively. When certain threshold levels on the training meter are reached, the sequence span length will either increase or decrease, thereby adapting to the participant's fluctuating WM span performance. Each day, participants complete three of the seven games, with games alternating on different days in order to maintain novelty and interest. For this pilot study, parents were instructed to devote about 15–30 min per day supporting their children through the training by providing encouragement and performance-based incentives, as well as redirecting attention when necessary. The training occurred 5 days a week, for approximately 5 wk. A phone session was conducted once a week to check in with each parent to discuss training progress and tailor reward plans, which mainly included primary reinforcers such as food but also included other rewards such as extra play time with an iPhone or skipping a chore. Reward schedules were largely left up to the parent's discretion based on the needs of the child, but typically consisted of small performance-based daily rewards, and a larger completion-based weekly reward.

Cogmed JM was originally designed for preschool-aged children between 4 to 6-year- old, and therefore is mental-age appropriate for most children and young teenagers with FXS. The graphics are child-friendly and include fuzzy monsters and stars that accumulate on the screen for every correct trial. Auditory feedback and encouragement are incorporated into the program and provided throughout the training. An animated aquarium is also presented at the end of each training session, with a new sea creature appearing each time. A demonstration program is available online (www.cogmed.com/jm.exe) that simulates the real training, but is capped at a span length of three items.

2.3. Analysis of baseline characteristics

We were interested in quantifying any cognitive/behavioral or demographic differences that may

exist between successful and unsuccessful participants among the 25 who attempted the initial demonstration program of Cogmed JM. A retrospective chart review was conducted, and all participants with data on the Stanford-Binet Intelligence Scales Fifth Edition (SBV) [34] and Vineland Adaptive Behavior Scales-Second Edition (VABS-II) [35] were included in the cognitive/behavioral profile analysis ($n = 15$). Four participants were excluded from the analysis due to partial or missing data. Six additional participants with intelligence quotient (IQ) ≥ 70 (i.e., without ID) were excluded because their mental age and level of maturity rendered Cogmed RM, the adolescent version, to be more appropriate for them than JM. Therefore, their performance on JM was not deemed to be comparable to that of others, and their IQs would unduly skew the average upwards. Furthermore, since the majority of individuals with FXS have ID, it is more informative and generalizable to only examine the cognitive/behavioral baseline characteristics within a sample with ID. Thus, we analyzed data on 9/17 successful participants and 6/8 unsuccessful participants.

No participant was excluded from the demographic analysis, however. We calculated chronological age, prevalence of co-morbid ASD as measured by the Autism Diagnostic Observation Schedule [36] and prevalence of concurrent ADHD medication between the two groups. ADHD diagnoses were made based on clinical history per DSM-IV guidelines by a licensed physician (study author Randi Hagerman) [37]. Medications were also prescribed by study author Randi Hagerman or by the individual's personal physician.

2.4. Evaluation of training success, load, and schedule

Among the eight participants enrolled in the 5-wk training, we analyzed training data that was automatically uploaded to the Cogmed server after each session. Training success was determined by in-game improvement on the trained working memory task. This was measured primarily by the index of improvement provided by Cogmed, as well as an analysis of daily changes in the average span length reached. The index of improvement is calculated by subtracting the start index, determined on days 2 and 3 of training, from the maximum index (determined by the highest span length reached on select exercises during any training day) [38]. Analysis of specific daily changes in average span length allowed us to also assess the training

load imposed upon WM in our sample, and how this changed over the course of the training period.

We also analyzed specific training schedules by looking at the number of training sessions completed, the total training period (number of days elapsed between the first and last training sessions), and the amount of time spent each day in training. Two participants were excluded from the training period analysis due to various breaks and holidays that unduly prolonged their training. One only completed 13 training sessions because he worked at a slower pace and typically spent two days completing each session. However, he still trained for the entire 5 wk period, and trained a roughly equivalent amount of time each day as the rest of the participants, despite only completing half a session (each session was within one standard deviation of average training time).

2.5. Evaluation of parental impressions

Among our training group of eight participants, we examined parental impressions regarding transfer of in-game improvements into more general domains of functioning. This was assessed by three behavioral rating scales given to parents pre- and post-training: the Aberrant Behavior Checklist-Community, the scoring algorithm of which has been modified and validated for the FXS population by Sansone et al. [39] to assess problem behaviors; the Swanson, Nolan, and Pelham Teacher and Parent Rating Scale to assess symptoms of ADHD [40]; and the Visual Analogue Scale to assess the following cognitive/behavioral domains selected by research staff: attention, hyperactivity, impulsivity, forgetfulness, organizing thoughts, and following directions. Change scores in rating scales were regressed onto each participant's Cogmed index of improvement to examine relationships between training progress and parental impressions of behavioral improvement after training.

2.6. Statistical analysis

We used Statistical Package for Social Sciences, version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) for the statistical analyses. Due to the small sample size, non-parametric analyses were utilized. The Mann-Whitney U test for independent samples test was used to compare differences between groups in the analyses of baseline characteristics. The Wilcoxon signed rank test for two related samples was

used to compare all intra-individual scores pre- and post-training. Correlational analyses were run using Spearman's rank-order test. Two-tailed P values ≤ 0.05 were considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Figure 1 shows the cognitive and behavioral profile of participants who successfully demonstrated understanding and compliance with task demands, compared to the profile of those who did not and were disqualified from the study. Successful participants all had higher baseline cognitive and behavioral profiles than unsuccessful participants. As shown in Table 1, this included higher adaptive behavior composites on the VABS-II ($P = 0.04$), as well as higher Full Scale IQ (FSIQ) ($P = 0.04$) and WM standard scores ($P = 0.04$) on the SBV.

No significant difference was found in medication usage ($P = 0.89$) or chronological age ($P = 0.16$) between successful and unsuccessful participants

(Table 1). Both groups were treated for ADHD to a similar extent and though unsuccessful participants were younger (10.01 ± 4.15 yr) than successful ones (12.49 ± 3.05 yr), the difference was not significant ($P = 0.16$). The unsuccessful group tended to have a higher prevalence of ASD (75%) than the successful (35%), but again the difference was not significant ($P = 0.12$; Table 1).

3.2. Training data

In-game performance data among the eight-trained participants demonstrated steady improvements over time on the Cogmed task (Figs. 2 and 3). Figure 2 shows a scatterplot of average Index of Improvement and training day, demonstrating a positive and significant correlation ($R^2 = 0.60$, $P < 0.01$). Figure 3 shows the average span level (defined as the length of the sequence to be held in WM), that participants reached during the training period, which typically fluctuated between two and three items. Training span, and consequently cognitive load, increased as the training period progressed. Both figures show average performance per day collapsed across all eight participants.

Figure 4 shows the average training schedules collapsed across the eight trained participants. Participants generally adhered to the standard Cogmed guidelines of 25 sessions in 5 wk, spending $23.85 \pm$
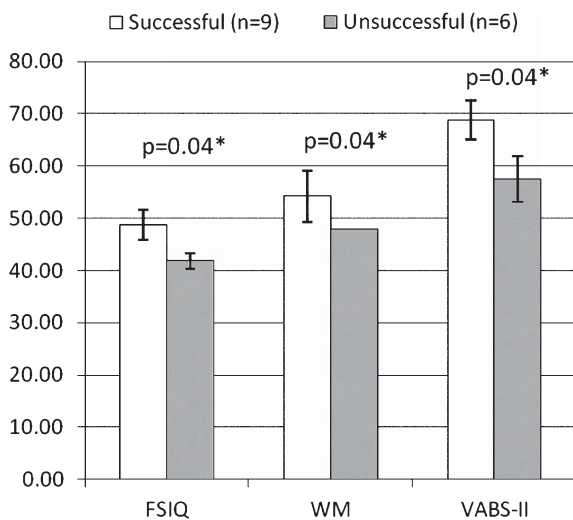

Fig. 1. Baseline profile of successful and unsuccessful participants. Baseline cognitive/behavioral profile of participants who were successful and unsuccessful with the Cogmed demonstration program. Full scale intelligence quotient, working memory and Vineland composite score-II were all significantly higher in the successful group. Only 15/25 participants had available data and intelligence quotient <70 and were included in the analysis. Intelligence quotient data was measured using the Stanford-Binet, 5th edition. Normative mean scores of all scales are 100, with standard deviations of 15. Error bars represent standard error of the mean.
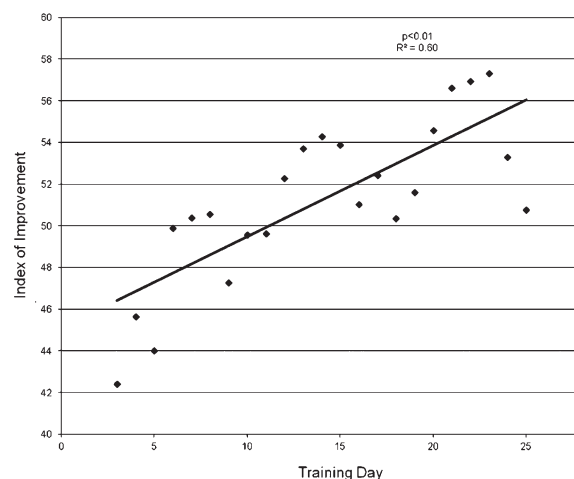

Fig. 2. Cogmed index of improvement scores across training period. Average index of improvement per session across all eight trained participants. One participant only trained 13 sessions, so sessions 14–25 are a composite of the other seven participants. Higher scores with increasing training days indicate consistent and incremental progress over the entire training period.
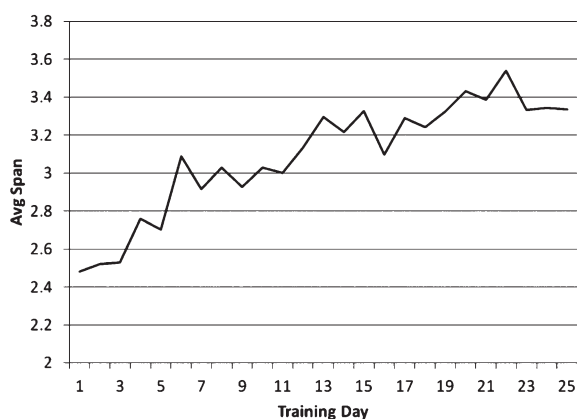
Fig. 3. Average span level across training period. Average span level achieved per session across all eight trained participants. One participant only trained 13 sessions, so sessions 14–25 are a composite of the other seven participants. On average, participants trained mostly with 2-3 item span lengths.
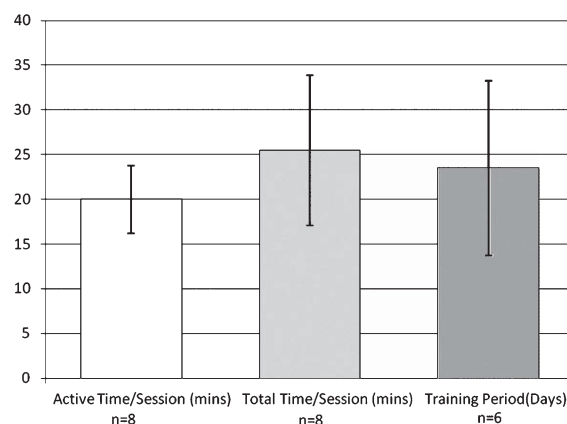

Fig. 4. Average training schedule. Average training schedule across all eight trained participants. Active time/session represents the amount of training time during which a participant is observing or responding to stimuli (excludes time for breaks and pauses). Total time/session includes breaks and pauses in addition to active time. Training period shows the number of days elapsed between the first and last days of training (inclusive). Two outliers were excluded from the training period analysis due to breaks and holidays. Error bars represent standard deviation.

7.58 total minutes (mean ± SD) each session (Fig. 4) and 19.10 ± 3.14 active minutes (mean ± SD), which excludes breaks and inter-trial pauses.

3.3. Parental impressions

Figures 5, 6, and 7 show average behavioral improvement across all participants, as reported by

parent rating scales. The Aberrant Behavior Checklist scores in Fig. 5 demonstrate significant improvement on the irritability ($P = 0.02$) and hyperactivity ($P = 0.02$) scales, and a trend on the Inappropriate Speech scale ($P = 0.09$). Figure 6 shows significant
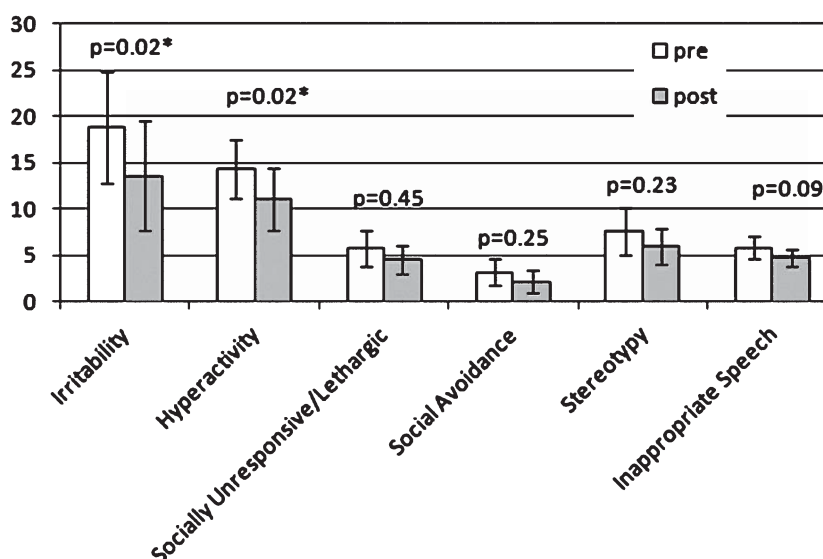

Fig. 5. Aberrant behavior checklist. Aberrant behavior checklist items, as reported by parents pre- and post-training, collapsed across all eight trained participants, and scored with the fragile-X syndrome specific rubric proposed by Sansone et al. [39] One participant's questionnaire was excluded due to failure of respondent to comply with instructions ($n = 7$). Lower scores indicate lower presence of aberrant behaviors. Irritability and hyperactivity were significantly improved post-training. Error bars represent standard error of mean.
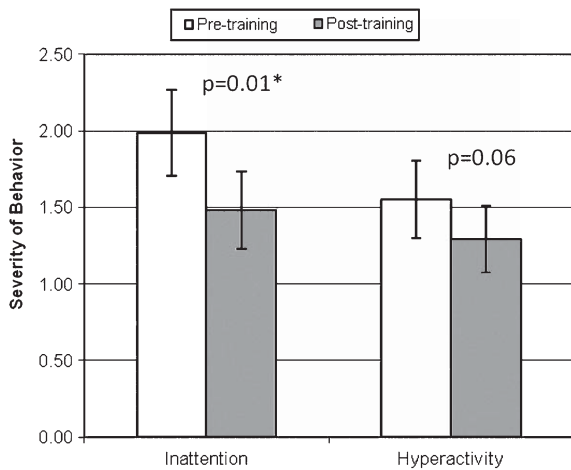
Fig. 6. Swanson, Nolan, and Pelham, Version IV (SNAP-IV). SNAP-IV attention deficit hyperactivity disorder rating scale, as reported by parents pre- and post-training, collapsed across all eight trained participants. Lower scores indicate less severe behavior. The inattention scale was significantly improved, while the hyperactivity scale showed a strong trend towards significance. Error bars represent standard error of mean.

improvement in the Swanson, Nolan, and Pelham, Version IV (SNAP-IV) Inattention domain ($P = 0.01$) and a trend towards significance in the hyperactivity domain ($P = 0.06$). The Visual Analogue scale in Fig. 7 shows significant improvement in attention ($P = 0.01$), impulsivity ($P = 0.03$) and organizing thoughts ($P = 0.04$).

Once again, the hyperactivity domain trended towards significance ($P = 0.07$). Correlations between behavioral rating scale change scores and Cogmed indices of improvement were not significant (Table 2).

4. Discussion

The purpose of this preliminary report is to explore the factors associated with a successful cognitive training experience in the FXS population. The primary finding is that a proportion of children with FXS can actively engage in the WM training, suggesting that it is reasonable to explore the effects of WM training on performance in future, placebo-controlled studies. Sixty-eight percent (17/25) of approached participants successfully demonstrated task competency (completing 2-item spans) on the Cogmed demonstration program available online, and 8/17 (47.06%) successful participants enrolled in and completed the 5 wk training program, showing small but consistent improvements throughout (Fig. 3).

We further sought to differentiate those participants who were able to demonstrate task competency from those who were not, based on their baseline cognitive and behavioral profiles. Though this current report is the first of its kind to explore this in FXS, Söderqvist et al. [28] used Cogmed JM in a population of general ID and found that higher baseline verbal working
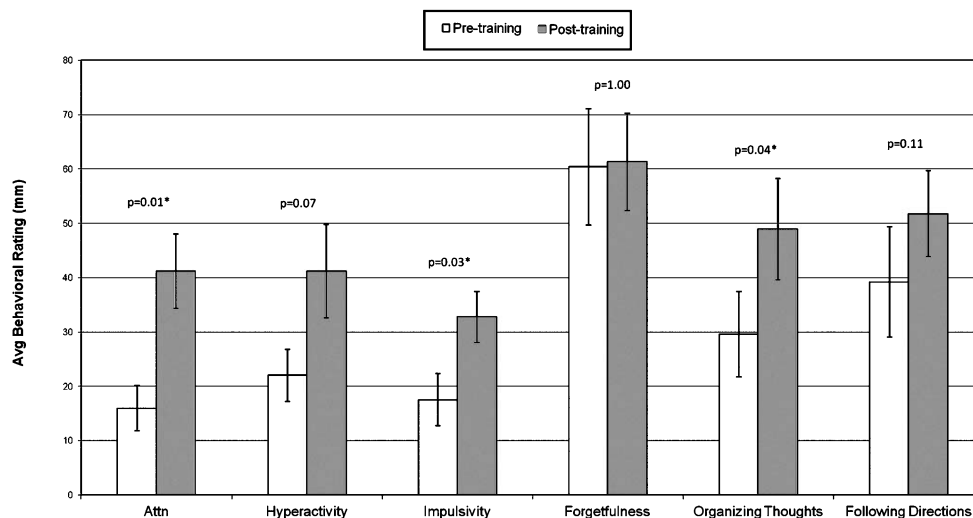

Fig. 7. Visual analogue scale. Parents were asked to mark off a spot on a 100 mm line to indicate the severity of each of the measured behaviors, pre- and post-training. Their mark was measured in mm from the start of the line. A higher score indicates a less problematic behavior. Scores were averaged across all eight trained participants. Attention, impulsivity, and organizing thoughts all improved significantly post-training. Error bars represent standard error of mean.

memory abilities, female gender, and lack of co-morbid diagnoses all predicted better outcomes. We found similar predictive variables in FXS. Those who were successful with the demonstration program all had significantly higher SBV, FSIQ, and WM scores. With only one exception, unsuccessful participants exhibited floored FSIQ scores of 40 and WM scores of 48 on the SBV. The only exception was a participant with a FSIQ of 51, who was successful after practicing on the demonstration program for 2 wk, and was subsequently enrolled in the study.

In addition to FSIQ and WM scores, successful participants also had significantly higher composite scores on the VABS-II compared to unsuccessful participants (Table 1). Furthermore, females were more likely than males to demonstrate task competency, similar to Söderqvist et al.'s [28] findings. In our study, all females (6/6) we approached were able to perform the demonstration tasks compared to only 8/19 (42.11%) males, but this is not unexpected considering females generally are higher functioning than males with FXS (29). Neither ADHD medication nor comorbid ASD were significant predictors of group differences. Despite the lack of statistical significance, it may still be clinically relevant to note that the prevalence of ASD within the unsuccessful group (75%) was about twice as high as that within the successful group (35%). A larger sample size may reveal true statistical differences that we are currently underpowered to detect.

Another aim of this study was to evaluate the most appropriate training schedule for the FXS population. Typically, the Cogmed JM schedule is 15–30 min a day, 5 days a week for 5 wk and most Cogmed JM training studies adhere to this general schedule. However, most of these studies have involved intellectually typical populations. It has yet to be determined what is reasonable to expect of a population with ID. For example, Van der Molen et al. [32] trained their cohort of adolescents with ID for only 6 min a day, three times a week, for 5 wk. Bennett et al. [33] found that a training schedule of 3 days/wk for 12 wk for between 18–30 min per day was more manageable for children with Down syndrome. While both these studies still resulted in successful training and transfer with their modified training schedules, the majority of participants in our study managed to successfully adhere to the standard Cogmed JM-recommended training schedule.

Furthermore, our data indicated that participants were actively engaged in the training task. Figs. 2 and 3 show that performance improved over time. More-over, when taking the difference between the highest and starting index of improvement scores derived from the training program, we get an average difference of 17.75 ± 6.76, which is comparable to JM normative data (mean $\pm$ SD $= 18.58 \pm 6.52$; 38). This provides evidence that participants were performing the task appropriately and were not simply clicking randomly. Parents also reported during weekly phone calls that their children generally enjoyed and understood the training tasks.

We note that although participants were engaged in the training, the overall cognitive load was still low, fluctuating typically between a span of two and three items (Fig. 3). Since individuals with FXS typically have profound WM impairments [41], it is possible that even such a low WM load can still produce training gains, as suggested by parental perception on questionnaires (Figs. 5–7). This is an important consideration for future training studies in FXS especially since most Cogmed placebo designs utilize a non-adaptive version of the active condition (i.e., the WM span is low and static, usually set at two items, and does not adjust based on the user's performance). It is presumed that the WM load of the placebo design is too low to result in any improvements, but in populations with ID such as FXS, WM capacity may be so constrained to begin with that even a low-load placebo condition may be sufficient to produce remediating effects.

In fact, previous research by Van der Molen et al. [32] assessing a group of adolescents with general ID detected improvement even in the non-adaptive group, which trained with a maximum span length of two items. This improvement was comparable to that of the adaptive group, which typically reached span lengths of three to four items. However, a very similar study in younger children with ID was conducted by Söderqvist et al. [28], which did not yield any significant improvements in their non-adaptive control group. A fundamental difference between the two studies, however, is that the Söderqvist et al. [28] control group trained at only a span of 1 item, a simple stimulus-response task that only weakly taps WM. The increase to two items in the study of Van der Molen et al. [32] may be substantial, especially for children with ID.

However, future studies in FXS or other populations with ID that use such a non-adaptive training condition as a placebo control (which is typical and standard for most Cogmed studies) may be able to partially account for the possibility of confounding treatment effects in the data analysis. One way could be

to examine differences in performance between those control participants who struggle more (i.e., produce more incorrect responses) and those who struggle less. It is likely that those who struggle more tax their WM more, even at a low load, and may be liable to see training gains even from the "placebo" condition. A study among cognitively-impaired participants with brain injury showed that those who start Cogmed training with a lower index score stand to gain the most out of training [42]. Thus, the baseline level of functioning could confound the data for populations such as FXS where participants starting at a lower index score may well receive quality training at or below the difficulty level of the placebo.

Finally, although the results of this pilot study suggest that Cogmed JM is a feasible intervention to implement in the FXS population, we cannot evaluate its efficacy given the small sample size, as well as the lack of appropriate controls and objective measures of cognitive changes. Nevertheless, our behavioral rating scales do show promise (Figs. 5–7) and parents reported significant improvements in one or more domains of each questionnaire.

This pilot study was conducted as a preliminary feasibility trial. Our results warrant further investigation into Cogmed's efficacy within the entire spectrum of the FXS population, including potentially the use of the more advanced Cogmed versions such as RM program (for older children and adolescents) that may be more appropriate for higher functioning individuals with FXS. To this end, a larger, randomized, placebo-controlled trial of Cogmed JM and RM is currently underway at our Center. WM training addresses a core cognitive deficit in FXS, and the results of this trial will serve to inform current clinical practices and may offer a powerful tool that may act synergistically with existing pharmaceutical targeted treatments that we hope will improve behavior, attention and cognition in FXS [43].

Conflicts of interest

Randi Hagerman has received funding from Novartis, Roche, Alcobra, and Neuren for treatment trials in FXS or autism. RH has also consulted with Genentech, Roche and Novartis regarding treatment trials in FXS. David Hessl has received funding from Novartis, Roche, and Seaside Therapeutics. Other authors declare no conflicts of interest.

Acknowledgments

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